REMARKS

Entry of the foregoing, reexamination and further and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 C.F.R. § 1.116, are respectfully requested.

By the foregoing amendment, claims 38, 40, 42-47, 49, 52-63, 65 and 68-78 have been canceled without prejudice or disclaimer of the subject matter recited therein. Further, claims 79-120 have been added. Support for the new claims can be found throughout the specification and in the previous claims. New claim 79 corresponds to previous claims 38 and 42. New claims 80 and 83 correspond to previous claim 40. New claim 86 corresponds to previous claim 38. New claims 87-90 correspond to previous claims 43-46, respectively. New claim 91 corresponds to previous claims 47 and 54. New claims 92 and 95 correspond to previous claim 49. New claims 98 and 99 correspond to previous claims 52 and 53, respectively. New claim 100 corresponds to previous claim 47. New claim 101 corresponds to previous claim 55. New claim 102 corresponds to previous claims 56 and 57. New claims 103-105 correspond to previous claims 58-60, respectively. New claims 106 and 107 correspond to previous claims 62 and 61, respectively. New claim 108 corresponds to previous claims 63 and 70. New claim 109 corresponds to previous claim 65. New claims 110-111 correspond to previous claims 68-69, respectively. New claim 112 corresponds to previous claim 63. New claim 113 corresponds to previous claim 71. New claim 114 corresponds to previous claims 72 and 73. New claims 115-119 correspond to previous claims 74-78, respectively, and new claim 120 corresponds to

previous claim 22. New claim 81 finds support on page 19, lines 6-8, of the specification. New claim 82 finds support on page 19, line 4, of the specification. New claim 84 finds support on page 18, lines 32-35, of the specification. New claim 85 finds support on page 18, lines 28, of the specification. New claim 93 finds support on page 19, lines 6-8, of the specification. New claim 94 finds support on page 19, line 4, of the specification. New claim 96 finds support on page 18, lines 32-35, of the specification, and new claim 97 finds support on page 18, line 28, of the specification. Accordingly, no new matter has been added.

I. Priority

The Examiner has acknowledged the claim to foreign priority. However, the Examiner has indicated that because a translation of the priority document has not been made of record, the teachings of Stanley et al. are available as prior art under 35 U.S.C. § 102(a). Applicants submit herewith an English translation of French application No. 96 09584.

II. Claim Objections

Claims 56, 57, 72 and 73 have been objected to under 37 C.F.R. 1.75(c) as allegedly being of improper dependent form for failing to further limit the subject matter of previous claims 55 and 71, respectively. Specifically, the Examiner has stated that claims 55 and 71 state that E6 has amino acids 111-115 deleted and E7 has amino acids 21-26

deleted and that the limitations in claims 56, 57, 72 and 73 are not further limiting. Applicants respectfully traverse this objection.

Applicants draw the Examiner attention to the fact that claims 55 and 71 (now claims 101 and 113) recite a E6 polypeptide of a human papillomavirus having amino acids 111-115 deleted and a E7 polypeptide of a human papillomavirus having amino acids 21-26 deleted, whereas claims 56, 57, 72 and 73 recite the same variants of polypeptides E6 and E7 but originating from HPV-16. In other words, dependent claims 56, 57, 72 and 73 further define the E6 and E7 variant proteins by naming the specific HPV strain (i.e., HPV-16) from which the E6 and E7 variant proteins are obtained. New claims 102 and 114 clarify the HPV-16 element that further defines the subject matter of claims 101 and 113.

Therefore, Applicants respectfully request withdrawal of the objection of claims 56, 57, 72 and 73.

III. Rejection under 35 U.S.C. § 112, second paragraph

Claims 38, 40, 42-47, 49, 52-63, 65 and 68-78 have been rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse this rejection.

The Examiner has stated that claim 38 is drawn to a pharmaceutical composition comprising at least one early and at least one late polypeptide of a papillomavirus, with the

exception of the specific combination E7 and L2 and that subsequent dependent claims 40 and 42 state that the early polypeptide is E6 and/or E7 and the late polypeptide is Ll and/or L2.

Further, the Examiner has stated that independent claims 47 and 63 include the combination E7 and L2 which is specifically excluded in independent claim 38. Based thereon, the Examiner has concluded that the compositions are contradictory in the independent claims and that it is unclear what Applicant intends.

This rejection is rendered moot in light of the cancellation of claims 38, 40, 42-47, 49, 52-63, 65 and 68-78. However, to the extent that this rejection applies to new claims 79-120, Applicants respectfully traverse this rejection.

New claims 79-120 recite specific combinations of HPV proteins described in the original disclosure, excluding de facto the E7 and L2 combination. Thus, this rejection does not apply to the new set of claims.

Finally, the Examiner has stated that the term " interleukin-2" found in claim 68 lacks antecedent basis. This "lack of antecedent basis" originates from a typographical error found in previous claim 63 (to which previous claim 68 refers) which recites at line 9 "interleukin-1" instead of "interleukin-2." Applicants stress that the term "interleukin-2" is supported throughout the specification. See, for example, page 5, line 36, of the specification. Correction of this typographical error has been introduced in new claim 108, which corresponds to previous claim 63.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 38, 40, 42-47, 49, 52-63, 65 and 68-78 under 35 U.S.C. § 112, second paragraph.

IV. Rejection under 35 U.S.C. § 112, first paragraph

Claims 38, 40, 42-47, 63, 65, and 68-78 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse this rejection.

The Examiner has stated that the exclusion of the specific E7 and L2 combination is not supported in the original claims and specification of the present application. Therefore, the Examiner has argued this limitation being new matter.

This rejection is rendered moot in light of the cancellation of claims 38, 40, 42-47, 49, 52-63, 65 and 68-78. However, to the extent that this rejection applies to new claims 79-120, Applicants respectfully traverse this rejection.

As discussed in section III above, new claims 79-120 recite specific combinations of HPV proteins described in the original disclosure, excluding de facto the E7 and L2 combination. Thus, this rejection does not apply to the new set of claims.

With respect to claim 63 (now claim 108), as discussed above, interleukin-1 is a typographical error introduced in the reply to the previous Official Action and this term

should therefore be replaced by "interleukin-2" which finds support throughout the original disclosure of the instant application.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 38, 40, 42-47, 63, 65, and 68-78 under 35 U.S.C. § 112, first paragraph.

V. Rejections under 35 U.S.C. § 102(a)

Claims 38, 40 and 42-46 have been rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Stanley et al. (WO 96/29091) for reasons of record. The Examiner has maintained that the teachings of Stanley et al. anticipate the present claims because the open language "comprising" does not exclude the addition of other materials within the composition, such as IL-12. Applicants respectfully traverse this rejection.

Applicants submit that Stanley et al. (WO96/29091) could not be properly used as prior art under 35 USC § 102(a) since this document was published on September 26, 1996. The present application properly claims benefit of priority to French patent application number 96 09584 filed on July 30, 1996, which was prior to the publication date of Stanley et al. (WO 96/29091). The Examiner has acknowledged the claim for foreign priority as well as the receipt of the certified copy of the priority document. To complete the entitlement to foreign priority, Applicants provide herewith an English translation of the French priority application number 96 09584. Therefore, Stanley et al. is not proper art.

Should the claims be rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Stanley et al. (U.S. Patent No. 6,096,869), Applicants submit that the new claims are now written to recite "consisting of."

Therefore, Applicants respectfully request withdrawal of the rejection of claims 38, 40 and 42-46 under 35 U.S.C. § 102(a).

VI. Rejections under 35 U.S.C. § 103(a)

Claims 38, 40, 42-47, 49, 52-54, 58-63, 65, 68-70 and 74-78 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Galloway (Infectious Agents and Disease, 1994, 3:187-193), Hines et al. (Obstetrics and Gynecology, 1995, 86(5):860-866), and Gajewski (Journal of Immunology, 1996, 156:465-472) for reasons of record. Applicants respectfully traverse this rejection.

The teachings of the documents cited by the Examiner were largely developed in Applicants' reply to the previous Official Actions. In summary, Galloway et al. teaches a composition comprising:

-an early papillomavirus polypeptide to treat HPV infections

-a late papillomavirus polypeptide(s) expressed as a fusion protein to prevent HPV infections, or

-a E7+L2 fusion protein.

Hines et al. discloses (1) a pharmaceutical composition intended for the prevention of a papillomavirus infection or tumor which comprises as therapeutic agent virus-like

particles made of late L1 and L2 HPV polypeptides and (2) a pharmaceutical composition intended for the treatment of papillomavirus-induced diseases relying on HPV-16 E7-derived peptides or cytototoxic T lymphocytes in vitro stimulated by a HPV early peptide and IL-2 (in other terms a cellular composition).

Gajewski relates to B7.1-induced stimulation of naive lymphocytes to cytotoxic T lymphocytes (CTL). To this end, the B7.1 CDNA was transfected into P815 mastocytoma cells. Mouse spienocytes were then stimulated with the transfected cells in the presence of an anti-CD3 antibody. B7.1 transfected tumor cells stimulated proliferation of CD4+ as well as CD8+ T cells. As discussed page 470, direct costimulation of CD8+ T lymphocytes by expression of B7.1 allows emergence of CTL that produce their own IL-2. It is suggested that expression of B7.1 on human tumor cells can render them better able to stimulate CD8+ lymphocytes and that utilization of B7.1-expressing autologous tumor cells may provide a plausible immunization approach for cancer patients. Again, Gajewski is primarily directed towards the use of a cellular composition comprising B7.1 transfected tumor cells to treat a cancer patient.

The objection concerning lack of inventive step does not apply to the new claims. In independent claim 79, the feature is the specific combination of E6 + E7 + L1 + L2 papillomavirus polypeptides. None of the cited documents disclose this specific combination. Rather to the contrary, the person skilled in the art would have used L1 or L2 capsid protein to provide protection against HPV infection or E5, E6 or E7 polypeptides to retard the development of HPV-induced tumors as taught by Galloway et al., or L1 and L2

capsid proteins as taught by Hines et al. There is no suggestion or motivation to combine the four specified papillomavirus polypeptides. It should be stressed that the sole attempt to combine one early and one late papilloma polypeptide (L2 and E7) fails to provide effective protection or treatment against HPV-induced diseases, as discussed previously. The inclusion of at least one immunostimulatory molecule in the E6 + E7 + L1 + L2 composition as specified in new claims 91-107 is not suggested either in Hines et al. or Gajewski which refer to cytokine stimulated lymphocytes. As indicated page 862 (end of second column) of Hines et al, "[t]he rationale for the therapy [i.e., the transfer of cytotoxic T lymphocytes stimulated by HPV early peptides] is that controlled in vitro stimulation of lymphocytes is more likely to yield effective anti-tumor responses compared to the response generated by the host in vivo." Therefore, Hines et al. teaches away from the present invention which relies on the administration of a set of HPV polypeptides and a cytokine to generate a immune response by the host in vivo. In this regard, the Examiner is directed to Example 6 of the instant application which clearly shows that the E6, E7, L1, L2 and IL-2-containing composition achieves prophylactic and therapeutic immunization in animal models against HPV-induced tumors.

In independent claim 108, the feature is the specific combination of E6 and E7 papillomavirus polypeptides and at least one immunostimulatory molecule selected from the group consisting of IL-2, IL-7, B7.1 and B7.2. None of the cited documents disclose the specific combinations as claimed. Indeed, Galloway illustrates inoculation of fibroblasts expressing either HPV E6 or E7 or vaccinia virus expressing the BPV E5, E6 or E7 genes

(see page 191 first column). Hines et al. discloses stimulation of an anti-HPV response either by E6 or E7-based peptide vaccination or by adoptive cellular immunotherapy with lymphocytes in vitro stimulated by HPV peptides and IL-2. As pointed out in our previous reply, the presence of IL-2 in the cultured lymphocytes is to develop their cytotoxic activity and IL-2 is not used as a therapeutic agent as such. As stated in the previous section, the controlled in vitro stimulation of lymphocytes is more likely to yield effective anti-tumor responses compared to the response generated by the host in vivo (in the absence of in vitro stimulation). Therefore on this basis, one skilled in the art would not have been motivated to administer a pharmaceutical composition combining E6 and E7 papillomavirus and at least one immunostimulatory molecule.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 38, 40, 42-47, 49, 52-54, 58-63, 65, 68-70 and 74-78 under 35 U.S.C. § 103(a).

Claims 56 and 57 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Galloway, Hines et al. and Gajewski as applied to claims 38-55 and 58-78 above, and further in view of Munger et al. and Crook et al. Applicants respectfully traverse this rejection.

The discussion regarding Galloway, Hines et al., and Gajewski above is incorporated herein by reference. With regard to Munger et al. and Crook et al., page 5, lines 2-6, of the present application states that Munger et al. and Crook et al. disclose the nononcogenic variants of the E6 and E7 HPV polypeptides.

As already discussed above, the combination of Galloway, Hines et al., and Gajewski do not render the claimed invention obvious. Munger et al. and Crook et al. in combination with the with Galloway, Hines et al., and Gajewski also do not render the claimed invention obvious.

As the specific combinations claimed in the pending independent claims are patentable, the patentability also applies to the dependent claims reciting a composition comprising the nononcogenic variants of the E6 and E7 HPV polypeptides.

Therefore, Applicants respectfully request withdrawal of the rejection of claims 56 and 57 under 35 U.S.C. § 103(a).

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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